REMARKS

Claims 1-73 were in this case. Claims 53-67, 72 and 73 are herein canceled as directed to a non-elected invention. Claim 2 is cancelled as redundant over amended claim 1. Claim 42 is herein canceled as redundant over claim 7. Claims 1, 3-5, 7-10, 12, 14, 18-26, 28, 32-41, 43-44, 50, 52, 68, and 70 have been amended herein. New claims 74-81 have been added. Claims 1, 3-41, 43-52, 68-71 and 74-81 are presently in this case.

This application contains drawings. The Office Action does not indicate whether or not the drawings submitted are acceptable. Applicants respectfully request acknowledgment that the drawings are acceptable as filed.

Applicants elected prosecution of the claims of Group I. New claims 74-81 read on that election. Claims 53-67, 72 and 73 are canceled as directed to a non-elected invention.

Independent claim 1 has been amended to replace the phrase "~~in~~ the presence of carboxylic acid groups" in the claim preamble with the phrase "which also contains one or more carboxylic acid groups or esters thereof". Peptides and proteins, as is known in the art, may contain carboxylic acid groups (terminal or side-chain), and/or amine groups (terminal or side-chain). The presence of carboxylic acids or esters thereof is noted in the preamble to emphasize the selective nature of the labeling method and to indicate that the method can be applied to esters of carboxylic acids. The term "carboxylic acid" has been broadened to "carboxylic acid and esters thereof." It is understood in the art that carboxylic acid groups in peptides and proteins may be esterified. This amendment is supported by the specification at page 7, lines 24-25.

In claim 1, the word "the" preceding "phosphate groups" has been replaced with "one or more" to emphasize that there may be one or more phosphate groups in the peptides or proteins to be selectively labeled. The "the" preceding "carboxylate" groups" in step a has been replaced

with the word "any" to emphasize that the peptide or protein to be selectively labeled may have any number of carboxylic acid groups or esters thereof.

In step a of claim 1 the protective group used for selectively labeling is recited to be "an amine."

In step b of claim 1 the words "bond" have been replaced with "bonds" to correct grammar and antecedent basis. The term "free phosphate groups" has been rewritten as "one or more free phosphate groups" to emphasize that one or more than one of such groups may be generated.

It is believed to be unnecessary to add the phrase "and esters thereof" in line 2 of step c of claim 1 because protection of carboxylic acid esters generates protected carboxylic acids.

The phrase "to thereby generate a peptide or protein in which the phosphate groups are selectively labeled or tagged" has been added at the end of claim 1 to better clarify the results of the method and to improve antecedent basis with dependent claims.

Claim 2 has been cancelled as redundant over amended claim 1.

Claim 3 has been amended to correct antecedent basis and clerical errors, for consistency with amended claim 1 and to replace "oligomer or polymer" with "peptide or protein."

Claim 4 has been amended for consistency with the amendments to claim 1. The claim has also been amended to better clarify that the amino group is a group on the amine that is a protective group and that the phosphate group is a group of the peptide or protein.

Claim 5 has been amended to correct claim dependency so that the claim now depends from claim 3. This amendment corrects antecedent basis with respect to "the solid support." The

claim has also been amended to better clarify that the "phosphate reactive group" (i.e., a group that rects with a phosphate) and the "second reactive group" are both groups on the linker.

Claim 7 has been amended for improved clarity to remove the word "amine."

Claim 8 has been amended for consistency with the amendment of claim 1.

Claim 9 has been amended to correct claim dependency to improve antecedent basis and to better clarify that the linker contains either a sulfhydryl group or a latent reactive group that can be transformed (e.g., by another reaction) into a sulfhydryl group.

Claim 10 has been amended to better clarify that the phosphate group is first reacted with cystamine which contains a latent reactive group (i.e., a latent free sulfhydral group) and that thereafter the cystamine is reduced to generate the sulfhydral reactive group.

Claim 12 has been amended to recite "a solid support material."

Claims 14 and 18 have been amended for proper antecedent basis with claim 1.

Claim 19 has been amended for improved clarity.

Claim 20 has been amended for proper antecedent basis and the term "corresponding" has been deleted as unnecessary because the claim recites that the peptide or protein labeled or tagged with the affinity label binds to the capture reagent.

Claim 21 has been amended to recite that step c in which the label or tag is reacted with the free phosphate groups comprises either attaching the labeled or tagged peptides or proteins to a solid support or binding the labeled or tagged peptides or proteins to a capture reagent.

Independent claim 22 has been amended to emphasize that the method can be used to detect phosphoproteins as well as phosphopeptides. This amendment is supported in the specification, for example, at page 5 lines 15-17. Step a of the claim has been amended to recite that the carboxylic acid groups are unprotected. This amendment emphasizes that after application of the step the carboxylic acid groups are unprotected. This language includes a step in which the carboxylic acid (and ester) groups may be protected at some time during the step. This amendment better clarifies that step a can be accomplished in the two step process as recited in claims 23 and 24. Claim 22 has further been amended in step b to recite "phosphate group" instead of "phosphate" for improved clarity. Step c of claim 22 has also been amended to improve the consistency of language within claim. Claim 22 and claims dependent therefrom have been amended to recite that esters of carboxylic acids can also be protected in step a. This amendment is similar to that made in claim 1 and is supported in the specification at page at page 7, lines 24-25.

Claims 23-24, 28, and 32-40 have been amended to provide for correct antecedent basis to claim 22.

Claim 24 has also been amended to emphasize that after initial protection the phosphate groups are selectively deprotected. The second recitation of the word "selective" in the last line of the claim has been removed as redundant.

Claim 25 has been amended to delete "a" which corrects a cleric error.

Claim 26 has been amended to delete the word "selectively" because it is redundant over the phrase "deprotected without cleavage of the amide bonds."

Claim 33 also has been amended to correct dependency so that it now depends from claim 32.

Claim 37 also has been amended to recite that carboxylic acids and their esters can be protected. The claim has been made dependent from claim 22.

Claim 41 has been amended to delete the word "group" to improve antecedent basis.

Claim 43 has been amended for improved antecedent basis by deleting the phrase "comprises a combination of" and reciting that the label is a differentially isotopically labeled protecting group. A differentially isotopically labeled protecting group is a combination in the sense that the protecting group carries different isotopes.

An obvious typographic error has been corrected in claim 44.

Claim 45 has been amended for consistency with amended claim 43.

Claims 50 and 52 have been amended for improved antecedent basis in view of amendment to other claims. Claim 52 has also been amended to replace the word "intensity" with "amount" which is believed to be more accurate. It is noted that relative intensities of fluorescence ate measured to obtain relate amounts of labeled materials.

Claims 68 and 70 have been amended to replace "the" with "any" refering to protection of any amine groups present in the peptides or proteins.

New claims74-81 have been added to better claim that which Applicants consider to be the invention. Claim 74 is supported by original claim 22. Claim 75 is supported by original claim 14. Claim 76 is supported by original claim 28. Claim 77 is supported by original claim 22 and original claim 1. Claim 78 is supported in the specification at page 21 , line 8 (digestion by trypsin give a tryptic digest). Claim 79 is supported by original claim 17. Claim 80 is supported by the original claims. Claim 81 is supported by original claim 7.

None of the amendments to the claims add new matter to the application.

The Rejections

Claims 1-52, 70 and 71 are rejected under 35 U.S.C.§ 112, first paragraph. The rejection is characterized as based on an allegation of inadequate written description. Applicants traverse the rejection as applied to claim 22 (and its dependents) and claim 1 (and its dependants).

Claim 44 is rejected to for the recitation of "hydroxy acid." The use of this term in the claims was the result of a typographic error. The term "hydroxy amine" which is described in the specification was intended. The claim has been amended and this rejection should be withdrawn.

Claim 1 is rejected with the statement (on page 4 of the Office Action):

> It is also not clear that the method of claim 1 would work in the absence of a preliminary protection of the amine group as shown in step 2 of Figure 1 since the unprotected amine would be expected to be affected by the reagents subsequently used in the method.

Contrary to the general statement of the rejection as based on inadequate written description. It appears, based on the above explanation of the rejection, that the Examiner doubts the operability of the method as claimed broadly in claim 1. Applicant stresses that the Office Action provides no scientific basis to support why it would not be clear to one of ordinary skill in the art that the method of claim 1 would operate in view of the teachings of the specification. Specifically, the Examiner has provided no reference or explanation as to why or how the unprotected amines would be affected by the reagents subsequently used. The specification clearly conveys that protection of amines in the peptides and proteins is optional, but preferred to avoid crosslinking of amine side chains. There is nothing on the record to show that the statement in the teaching in the specification that this step is optional is inconsistent with any general principles in the art. In the absence of such reasoning, the statements in the specification should be believed. See In re Marzzochi, 169 USPQ 367 (CCPA, 1971).

With respect to the adequacy of the written description, the specification does not state that protection of amine groups is required. On page 15 lines 11-15 of the specification, it is clearly stated that amine groups are protected in a specific embodiment or a preferred embodiment. The scheme of Figure 1 is stated to illustrate the invention. On page 31, lines 1-7, it is clearly conveyed that amine protection is optional, but preferred to avoid "crosslinking of amine side chains during sample preparation." The presence of amine groups on a peptide or protein does not interfere with the reactions with the protective groups that are used to form "phosphoramide bonds" or "amide bonds" or with the selective cleavage reaction used to cleave phosphoramide bonds to regenerate free phosphate groups. It is known and understood in the art that carboxylic acid (and ester) groups and phosphate groups have reactivites that are significantly different from amine groups. It may be that in many cases the method of the invention will exhibit improved results, when the optional amine protection step is employed. However, the amine protection step is not essential for the operation of the steps as claimed in claim 1.

The specification as a whole describes that the use of an amine protection step is optional, albeit preferred. There is no requirement that an applicant claim only the preferred method of an invention. Thus, the written description provided in the specification is consistent in scope with claim 1 and its dependents.

Applicants submit that claim 1 meets both the enablement and written description requirement of § 112, first paragraph.

Claim 22 was rejected based on the statement (on page 3 of the Office Action):

> There is no enabling written description in the specification of how to perform the method of claim 22 wherein the phosphate group is not protected prior to its being selectively labeled ... , i.e., there is no enablement for how to actually perform the method of claim 22 as described at page 7, lines 1-17 and page 10, line 23 *et seq*

of the specification. The enabling written description of the invention as set forth in the specification is limited to the method of claim 1 wherein a reagent is used which protects both the carboxylic acid and the phosphate groups which are then labeled. (emphasis in the original)

The explanation of the rejection continues (page 3, 3 lines from the bottom of the page):

The method described in Example 2 of the specification involves the isotopic labeling of the carboxylic acid groups in the presence of unprotected phosphate groups but does not involve any labeling of the phosphate groups per se as is required by claim 22.(emphasis in the original)

Applicants have amended claim 22 to replace the phrase "remain unprotected" with "are unprotected" in reference to "phoshate groups." The intent of the amendment is to emphasize the results of the application of the step rather than to import any particular mechanism by which the resultant "unprotected" phosphate groups are generated.

Again it is not clear to Applicants if the rejection of claim 22 and its dependents is based on an allegation of inadequate enablement or inadequate written description. It is well established that the two requirements are distinct. In either case, the rejection has not provided any scientific basis or reasoning to support an allegation (1) that one of ordinary skill in the art would doubt that the inventors had possession of the invention as described (on pages 7 and 10) at the time of filing or (2) why one of ordinary skill in the art could not practice the invention as claimed (i.e., what was lacking in the enabling description). Applicants submit that one of ordinary skill in the art in view of the teachings and examples provided could by routine testing of known reagents identify reagents in addition to those exemplified to carry out the selective labeling as claimed in Claim 22. Applicants further submit that the description examples and teachings of the specification in view of what is known to one of ordinary skill in the art provide a fully enabling teaching of the method as claimed in claim 22. The rejection as it applies to

enablement should be withdrawn. Further, because there is no scientific basis or reasoning given in the Office Action to support a finding of lack of enablement, the rejection is improper and should be withdrawn.

Page 7, lines 1-17 and page 10, beginning at line 23, provide a written description of the method of claim 22 commensurate in scope with that claim. The two step method of claim 1 is one example of a method that can be used to selectively label carboxylic acid groups (and their esters) of a peptide or protein and regenerated free phosphate groups of the peptide or protein. The Office Action gives no explanation as to why the clear statements in the specification accompanied by concrete examples would not be understood by one of ordinary skill in the art that the inventors had possession of the invention as claimed in claim 22. The rejection as it applies to the adequacy of the written description should be withdrawn.

With respect to the Examiner's comment on Example 2. The method of Example 2 refers back to the selective labeling method of Example 1 and does involve labeling of phosphates and regeneration of free phosphate. Applicants note that the specification provides a specific example of the labeling of phosphate groups as in step b of claim 22, employing cystamine (See Example 1).

Applicants have added new claim 80 which should be considered adequately described and enabled by the Examiner in view of the comments in the Office Action concerning claim 22. New claim 80 contains the two step selective labeling process of claim 1 (steps a and b). Applicants submit, referring to arguments above regarding claim 1, that claim 80 is both adequately enabled and described in the specification of this application.

Claims 1-52 and 68-71 have been rejected under 35 U.S.C.§ section 112, second paragraph as indefinite. Most of the issues raised by the Examiner have been addressed by amendment. Each of the items raised in paragraphs 6a-u will be discussed below.

Regarding 6a: The phrase "in the presence of carboxylic acid groups" has been deleted from claim 1. The intent of the phrase, as is clear from the balance of the claim, was to refer to carboxylic acid groups in peptides and proteins. It is believed that the phrase was redundant over language in the claim and has been deleted.

Regarding 6b: The phrase "oligomer or polymer" was a clerical error in claim 3 and has been corrected.

Regarding 6c: Proper antecedent basis in claim 4 has been provided by amendment. It has been better clarified that the amino group is that of the protective group that is an amine and that the phosphate group is that of the peptide or protein.

Regarding 6d and 6e: Antecedent basis has been corrected by correcting claim dependency in claim 5. The amendment of claim obviates the rejection with respect to claim 7.

Regarding 6f: The term "amine protective group" was intended to refer to a protective group that is an amine. Claim 7 has been amended to clarify this intent.

Regarding 6g: Claim 9 has been amended to better clarify free phosphate groups are reacted with a linker in reference to step c of claim 1. The linker contains a sulfhydryl group or a latent reactive group that can be transformed into a sulfhydryl group. The amendment of claim 1 in part obviates the rejection. Dependancy is believed to be correct.

Regarding 6h and 6i: Claim 10 is not inconsistent with claim 9. Cystamine is a linker that contains a latent reactive group. The language of amended claim 10 emphasizes this. The generation of a free sulfhydral group is part of the indirect linking of free phosphate groups to a label via a linker.

Regarding 6j: Claim 12 has been amended to recite "a solid support material" which is believed to obviate the rejection.

Regarding 6k: The term "reactive label" is defined in the specification at page 11, lines 1-2 as a label "which carries at least one reactive group or at least one latent reactive group."

Regarding 6l: Claim 21 has been amended to recite that step c comprises a step of attachment. Applicants point out that selective attachment of a material to a solid support or a capture reagent facilitates separation of the attached material from non-attached material. Separation can be accomplished, for example, by removing the solid material (with attached peptide or protein) from unattached peptides and proteins. New claims 75 and 76 are directed to methods including separation.

Regarding 6m: Claims 18-20 have been amended to recite "selectively labeled or tagged peptide or protein " in place of "phosphopeptide." Claim 21 has been amended to recite "peptide or protein having free phosphate groups" in place of "phosphopeptide."

Regarding 6n: Most generally claim 22 relates to the detection of phosphopeptides and phosphoproteins as differentiated from peptides and proteins that do not carry phosphate groups. However, the detection of the label in step c can in specific embodiments (e.g., claims 47 or 48) further comprise identification of an individual phosphopeptide or phosphoprotein.

Regarding 6o: In claim 22 the phrase "remain unprotected" has been replaced with "are unprotected" to refer to the state of protection after the application of the step. The step as amended clearly encompassed a two step process, such as that of claim 23, in which both groups are protected followed by selective deprotection.

Regarding 6p: Step b of claim 22 generates selectively labeled phosphopeptides and phosphoproteins. Claim 32 has been amended to recite that "the selectively labeled

phosphopeptides or phosphoproteins" are separated "from the mixture of peptides or proteins in a sample" prior to detection step c.

Regarding 6q: Claim 33 now depends from claim 32.

Regarding 6r: Claim 37 now depends from claim 22. It is clear from the language of the claim as amended that differentially isotopically labeled protecting groups for carboxylic acids or esters thereof are employed with different samples.

Regarding 6s: Claim 41 has been amended to delete "group."

Regarding 6t: Claim 43 has been amended to recite that the protecting group is a differentially isotopically labeled protecting group.

Regarding 6u: Claim 44 has been amended to recite "hydroxy amine."

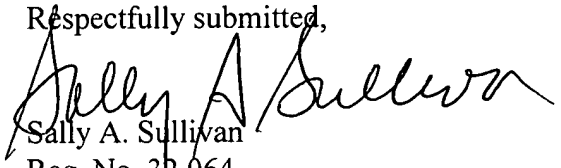
In view of the amendments and the foregoing arguments the rejections under 35 U.S.C. § 112, second paragraph should be withdrawn.

Conclusion

All of the claims currently pending in this case are believed to be allowable and passage to issuance is respectfully requested.

This amendment is accompanied by a Petition for Extension of Time for three months and requisite fee. It is believed that no additional fees are required. If this is incorrect, please deduct the appropriate fee from deposit account 07-1969.

Respectfully submitted,



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